Relationship Between Tumor Response and Tumor-Related Symptoms in *RAS* Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses From 3 Panitumumab Trials

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Abstract

Tumor-related symptoms can affect treatment choices in metastatic colorectal cancer (mCRC). In the current study, 659 patients with *RAS* wild-type mCRC were retrospectively analyzed to evaluate the relationship between tumor shrinkage and the time to onset of tumor-related symptoms. Symptom onset was delayed in patients with earlier and greater tumor shrinkage. Therefore, treatments that facilitate cytoreduction may delay symptom development.

Background: There is no standardized assessment of symptomatic events in metastatic colorectal cancer (mCRC) despite disease symptoms that affect treatment decisions. Data from 3 first-line panitumumab in mCRC trials were retrospectively analyzed to assess whether early tumor shrinkage (ETS) and depth of response (DpR) were associated with time to occurrence of tumor-related symptoms. **Patients and Methods:** Patients with *RAS* wild-type mCRC from PRIME, PEAK, and Study 314 were included. ETS was defined as a reduction of $\geq$ 30% in the sum of the longest diameters of lesions at 8 weeks. DpR was calculated as maximum percentage change in tumor size from baseline to nadir. The proportion of patients who developed symptoms (including a composite symptomatic endpoint) during study treatment was calculated. This study was registered at ClinicalTrials.gov as PRIME (NCT00364013), PEAK (NCT00819780), and Study 314 (NCT00508404). **Results:** Overall, data of 659 patients were analyzed. Onset of symptoms was delayed in patients with ETS $\geq$ 30% versus ETS $<$ 30% and in patients with greater DpR. In patients with symptoms at baseline who experienced ETS $\geq$ 30%, overall survival was similar to that seen for patients without symptoms at baseline. **Conclusion:** Both ETS and DpR were associated with delayed onset of symptoms in *RAS* wild-type mCRC patients. Treatments with high cytoreductive potential may delay symptom development.

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Introduction

Colorectal cancer is the third most diagnosed cancer worldwide, leading to an estimated 850,000 deaths in 2018.[1] Metastatic colorectal cancer (mCRC) is only curable in a subset of patients by complete surgical resection. Systemic therapy is the most appropriate treatment option for most patients with mCRC; it primarily focuses on prolonging survival and improving quality of life (QoL). Conventional chemotherapy usually involves fluoropyrimidine-based regimens containing irinotecan or oxaliplatin, such as fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and fluorouracil, leucovorin, and irinotecan (FOLFIRI).[2] In certain patients, targeted therapies may also be provided. These include epidermal growth factor receptor (EGFR) inhibitors (eg, panitumumab, cetuximab), vascular endothelial growth factor (VEGF) inhibitors (eg, bevacizumab, aflibercept), and VEGF receptor inhibitors (eg, regorafenib, ramucirumab).[2]

Panitumumab is approved in Europe, the United States, and elsewhere for the treatment of patients with *RAS* wild-type (WT) mCRC.[3,4] In Europe in the first-line setting, panitumumab is indicated for use in combination FOLFOX or FOLFIRI on the basis of the results of 2 randomized controlled trials (PRIME, phase 3; and PEAK, phase 2) and a single-arm phase 2 study (Study 314).[5-10] Importantly, systemic therapy can result in tumor shrinkage, which may enable patients with previously unresectable disease to undergo curative surgery (often referred to as conversion therapy).[11,12]

Recent retrospective analyses of clinical trial data in mCRC have included investigation of newer measures of tumor response, including early tumor shrinkage (ETS) and depth of response (DpR).[11,13-15] For example, in the phase 3 PRIME trial, which compared first-line panitumumab plus FOLFOX4 with FOLFOX4 alone in patients with previously untreated mCRC, patients in both treatment arms who experienced ETS $\geq$ 30% by 8 weeks showed longer overall survival (OS) than those who did not (panitumumab plus FOLFOX4 arm: 34.5 vs. 18.2 months; $P < .0001$; FOLFOX4 alone arm: 30.7 vs. 16.0 months; $P < .0001$), indicating the prognostic utility of ETS regardless of treatment received.[11] In the same trial, patients with tumor-related symptoms at baseline (defined as EQ-5D pain/discomfort scale score > 1) who experienced ETS $\geq$ 30% demonstrated a statistically meaningful improvement in QoL compared to those who did not experience ETS $\geq$ 30.[16] Both ETS and DpR have been associated with improved progression-free survival, OS, and resection rates, irrespective of treatment received, in a retrospective analysis of 3 first-line panitumumab mCRC studies.[14] In the same study, patients who received panitumumab in PRIME and PEAK (which compared panitumumab plus modified FOLFOX [mFOLFOX6] with bevacizumab plus mFOLFOX6) had higher ETS $\geq$ 30% rates (PRIME: 59% vs. 38%; PEAK: 64% vs. 45%) and greater DpR (PRIME: 54% vs. 46%; PEAK: 65% vs. 46%) than those who received treatment without panitumumab.[14] An association between both ETS and DpR and survival outcomes has also been observed in retrospective and prospective trials of cetuximab.[13,17-19] In the CRYSTAL and OPUS trials, which evaluated cetuximab with and without FOLFIRI and FOLFOX4, respectively, ETS was significantly associated with progression-free survival in both the cetuximab plus chemotherapy and chemotherapy-alone treatment arms.[13] In retrospective analysis of the TRIBE trial, treatment with fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab versus FOLFIRI plus bevacizumab improved ETS and DpR, and both response parameters predicted survival.[13,15,17-19]

Tumor location has also been highlighted as an important factor to consider in treatment decisions for mCRC. Left-sided tumors are more common and are associated with a better prognosis and increased response to anti-EGFR treatment.[20-22] First-line panitumumab treatment has been associated with improved ETS and DpR compared to comparator treatments in patients with left-sided disease.[21] Further to this, existence of ETS $\geq$ 30% may identify patients with right-sided tumors that might respond to panitumumab.[21]

In addition to tumor response, patients' QoL and tumor-related symptoms should be factored into treatment decisions in mCRC.[2] Common tumor-related symptoms of advanced cancer include pain, anorexia, fatigue, and asthenia.[23,24] It is recommended that patients with severe symptoms receive intensive treatment to improve symptoms and avoid rapid deterioration, and hence prolong survival.[2] However, there is currently no standardized assessment of symptomatic events, and therefore the treating physician is responsible for deciding which symptoms are relevant to each patient.

Here we present the results of new retrospective analyses of 3 clinical studies of first-line panitumumab therapy in mCRC (PRIME, PEAK, and 314). These analyses aim to investigate whether the occurrence of ETS and DpR in response to treatment may be related to the time to occurrence of new symptoms during the treatment period. As part of this work, we developed a novel composite endpoint for modeling tumor-related symptoms.[25]

Patients and Methods

Study Designs

PRIME (ClinicalTrials.gov NCT00364013) was a randomized phase 3 study in which patients received panitumumab (6 mg/kg every 2 weeks) plus FOLFOX4, or FOLFOX4 alone (n = 1183).[5,6] PEAK (NCT00819780) was a randomized phase 2 study comparing mFOLFOX6 in combination with panitumumab (6 mg/kg, every 2 weeks) or bevacizumab (5 mg/kg every 2 weeks) (n = 285).[9,10] Study 314 (NCT00508404) was a single-arm phase 2 study of patients treated with panitumumab (6 mg/kg, every 2 weeks) plus FOLFIRI (n = 154).[7,8] All 3 studies recruited adult patients with previously untreated mCRC.[5-10] The current analyses include patients with *RAS* WT mCRC only (ie, patients were excluded if their tumors contained mutations in *KRAS* or *NRAS* exons 2 [codons 12/13], 3 [codons 59/61], and 4 [codons 117/146]) who had data assessable for ETS.

All study procedures were performed in accordance with accepted ethical standards, including the Declaration of Helsinki, and all patients provided written informed consent. Separate consent was not needed for these retrospective analyses.

Analyses

For each study, the proportion of patients with the symptoms listed below and the proportion who developed the following symptoms during study treatment (panitumumab or bevacizumab plus chemotherapy or chemotherapy alone) was calculated: new

opiate use (derived from concomitant medication start and stop dates); first weight loss event (weight decrease of ≥ 10% vs. baseline or occurrence of relevant adverse events); new anemia-type event (concomitant medicines for anemia provided during treatment [excluding prophylaxis], blood transfusion, hemoglobin < 90 g/L, or relevant adverse events); or new asthenia-type event (derived from relevant adverse events). Further details of the symptom definitions used are provided in Supplemental Table 1 in the online version. A composite symptomatic endpoint was also analyzed that included any symptom listed above. The proportion of patients who experienced a decline in Eastern Cooperative Oncology Group performance status (ECOG PS; time to first ECOG PS score greater than baseline) was also calculated, though this was not included in the composite endpoint as any symptom can affect ECOG PS. Because of their low clinical relevance, grade 1 events were excluded from the analyses.

Time to occurrence of new symptomatic events and ECOG PS decline were analyzed by ETS status for individual and pooled studies using the Kaplan-Meier method. ETS was defined as reduction of ≥ 30% in the sum of the longest diameters of measurable target lesions (which also defines a partial response according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1)[26] at 8 weeks after initiation of study treatment. Time to occurrence of new symptomatic events across the pooled studies was also analyzed according to DpR using the Kaplan-Meier method. DpR was calculated as the maximum percentage change from baseline to nadir in patients who had tumor shrinkage. DpR had a positive value for tumor reduction, negative for tumor growth, and 0 for no change. Patients with tumor growth were categorized as having DpR < 0%. Patients with tumor reduction were subdivided into 4 categories on the basis of the extent of shrinkage. These included the RECIST v1.1 cutoff for a partial response (30%)[26] and 3 approximately equal-size groups divided by quartiles: 0-30%, 31-52%, 53-72%, and 73-100%.

A Cox proportional hazards model was used to calculate hazard ratios (HRs). Kaplan-Meier medians and adjusted HRs are presented with 95% confidence intervals (CI) and HR *P* values.

Results

Patients

A total of 659 patients (41% of the total number of participants across the 3 trials) were included in the analyses. Across the pooled studies, 29% (194/659) had a tumor-related symptom (as assessed by the composite endpoint) at baseline, and 41% (270/659) had baseline ECOG PS ≥ 1. Overall, 84% (553/659) developed a tumor-related symptom or experienced ECOG PS decline during the study treatment.

Patients were categorized into 2 groups on the basis of ETS status: ETS < 30% (n = 330 [PRIME: n = 227; PEAK: n = 70; 314: n = 33]) and ETS ≥ 30% (n = 329 [PRIME: n = 213; PEAK: n = 84; 314: n = 32]). Across the 3 studies, baseline patient demographics and disease characteristics were generally similar for patients with ETS < 30% or ETS ≥ 30%, although patients with ETS < 30% were more likely to have *BRAF* mutations, and patients with ETS ≥ 30% were more likely to have undergone resection and to have better baseline ECOG PS (Table 1). The number and proportion of patients in each study who had symptoms at baseline (or events indicative of symptoms) and who developed further symptoms during the study, by ETS status, is provided in Supplemental Table 2 in the online version. ECOG PS at baseline and the proportion of patients who experienced ECOG PS decline during the study period are also shown. In pooled analysis, the proportion of patients who experienced each new symptomatic event and ECOG PS decline was lower or the same in patients who experienced ETS ≥ 30% versus those who did not (ETS < 30%): new opiate use (34.3% vs. 38.8%), new weight loss event (42.6 vs. 46.1%), new anemia-type event (16.4% vs. 22.4%), new asthenia-type event (59.3% vs. 60.3%), and ECOG PS decline (47.4% vs. 47.6%) (Supplemental Table 2 in the online version).

Time to New Symptomatic Events by ETS and DpR

In pooled analysis, for the composite endpoint, median (95% CI) time to onset of any of the assessed symptoms was delayed in patients with ETS ≥ 30% versus those with ETS < 30% (5.0 [3.9-7.0] vs. 3.4 [2.8-4.6] months; HR [95% CI], 0.80 [0.66-0.97], $P = .0213$) (Figure 1A, Table 2). Furthermore, 46.1% and 35.0% of patients with ETS ≥ 30% did not experience a symptom, as assessed by the composite endpoint, at 6 or 12 months, respectively, compared to 39.6% and 28.6% of patients with ETS < 30% (Table 2). Greater DpR was also associated with delayed onset of any of the symptoms included in the composite endpoint (4.9 vs. 1.5 months for DpR 73-100% vs. DpR < 0%; HR [95% CI], 0.49 [0.33-0.73], $P = .0004$) (Figure 1B).

ETS ≥ 30% was significantly associated with delayed onset of new opiate use (HR [95% CI], 0.71 [0.55-0.92], $P = .0090$), first weight loss event (HR [95% CI], 0.64 [0.48-0.85], $P = .0022$), new anemia-type event (HR [95% CI], 0.60 [0.41-0.88], $P = .0079$), and new asthenia-type event (HR [95% CI], 0.77 [0.60-1.00], $P = .0492$) (Figure 2, Table 2). For each individual symptom, more patients with ETS ≥ 30% did not have a selected symptom at 6 or 12 months, compared to patients with ETS < 30% (Table 2). The median time to ECOG PS decline was numerically longer for patients with ETS ≥ 30% (13.9 months) than for those with ETS < 30% (7.9 months; HR [95% CI], 0.87 [0.69-1.08], $P = .2042$) (Table 2, Supplemental Figure 1 in the online version), but this did not achieve statistical significance. Time to new symptomatic events and ECOG PS decline according to ETS status were consistent across each individual study analyzed (Supplemental Figure 2 in the online version).

Time to New Symptomatic Events by ETS and DpR for Patients With and Without Symptoms at Baseline

Baseline patient demographics and disease characteristics by ETS status for the subgroup of patients who were symptomatic at baseline (29% [194/659]) are shown in Supplemental Table 3 in the online version. The existence of tumor-related symptoms at baseline was associated with a poorer prognosis; OS was reduced in these patients compared to patients with no symptoms at baseline (median [95% CI], 21.2 [18.0-24.3] vs. 27.8 [24.0-30.3] months; HR [95% CI], 1.30 [1.08-1.56], $P = .0054$) (Figure 3A). However, patients with tumor-related symptoms who experienced ETS ≥ 30% had OS similar to that of patients with no symptoms at baseline who experienced ETS ≥ 30% (median [95% CI], 31.7 [23.8-41.9] vs. 36.4 [31.7-41.2] months; HR [95% CI], 1.10 [0.80-1.49], $P = .5671$) (Figure 3B).

Table 1 Patient Baseline Demographics and Disease Characteristics by ETS Status

Characteristic	PRIME		PEAK		Study 314		All Subjects	
	ETS ≥ 30% (N = 213)	ETS < 30% (N = 227)	ETS ≥ 30% (N = 84)	ETS < 30% (N = 70)	ETS ≥ 30% (N = 32)	ETS < 30% (N = 33)	ETS ≥ 30% (N = 329)	ETS < 30% (N = 330)
Age (y), median (range)	60 (28-82)	62 (24-80)	60 (23-77)	61 (39-82)	63 (44-84)	67 (38-79)	60 (23-84)	62 (24-82)
Sex								
Female	72 (33.8)	77 (33.9)	29 (34.5)	22 (31.4)	6 (18.8)	6 (18.2)	107 (32.5)	105 (31.8)
Male	135 (63.4)	147 (64.8)	54 (64.3)	48 (68.6)	25 (78.1)	27 (81.8)	214 (65.0)	222 (67.3)
Treatment								
Panitumumab + FOLFIRI	0	0	0	0	31 (96.9)	33 (100.0)	31 (9.4)	33 (10.0)
Panitumumab + FOLFOX	127 (59.6)	88 (38.8)	0	0	0	0	127 (38.6)	88 (26.7)
Panitumumab + mFOLFOX6	0	0	50 (59.5)	29 (41.4)	0	0	50 (15.2)	29 (8.8)
Bevacizumab + mFOLFOX6	0	0	33 (39.3)	41 (58.6)	0	0	33 (10.0)	41 (12.4)
FOLFOX alone	80 (37.6)	136 (59.9)	0	0	0	0	80 (24.3)	136 (41.2)
***BRAF* Status**								
Mutant	10 (4.7)	36 (15.9)	5 (6.0)	6 (8.6)	1 (3.1)	7 (21.2)	16 (4.9)	49 (14.8)
Wild type	196 (92.0)	186 (81.9)	79 (94.0)	64 (91.4)	31 (96.9)	26 (78.8)	306 (93.0)	276 (83.6)
Unknown	7 (3.3)	5 (2.2)	0	0	0	0	7 (2.1)	5 (1.5)
Baseline ECOG PS								
0	132 (62.0)	116 (51.1)	58 (69.0)	40 (57.1)	17 (53.1)	14 (42.4)	207 (62.9)	170 (51.5)
1	68 (31.9)	91 (40.1)	25 (29.8)	30 (42.9)	13 (40.6)	17 (51.5)	106 (32.2)	138 (41.8)
2	7 (3.3)	16 (7.0)	0	0	1 (3.1)	2 (6.1)	8 (2.4)	18 (5.5)
Missing	6 (2.8)	4 (1.8)	1 (1.2)	0	1 (3.1)	0	8 (2.4)	4 (1.2)
Resection	42 (19.7)	19 (8.4)	15 (17.9)	8 (11.4)	7 (21.9)	2 (6.1)	64 (19.5)	29 (8.8)
Complete	33 (15.5)	11 (4.8)	12 (14.3)	4 (5.7)	3 (9.4)	1 (3.0)	48 (14.6)	16 (4.8)
Sites of Metastasis								
Liver + other	135 (63.4)	156 (68.7)	41 (48.8)	26 (37.1)	14 (43.8)	17 (51.5)	190 (57.8)	199 (60.3)
Liver only	52 (24.4)	26 (11.5)	26 (31.0)	16 (22.9)	15 (46.9)	9 (27.3)	93 (28.3)	51 (15.5)
Other only	20 (9.4)	42 (18.5)	16 (19.0)	28 (40.0)	2 (6.3)	7 (21.2)	38 (11.6)	77 (23.3)
Tumor Side								
Left	161 (75.6)	136 (59.9)	53 (63.1)	48 (68.6)	24 (75.0)	20 (60.6)	238 (72.3)	204 (61.8)
Right	27 (12.7)	49 (21.6)	15 (17.9)	16 (22.9)	2 (6.3)	3 (9.1)	44 (13.4)	68 (20.6)
Unknown	25 (11.7)	42 (18.5)	16 (19.0)	6 (8.6)	6 (18.8)	10 (30.3)	47 (14.3)	58 (17.6)

Table 1 Continued

Characteristic	PRIME		PEAK		Study 314		All Subjects	
	ETS ≥ 30% (N = 213)	ETS < 30% (N = 227)	ETS ≥ 30% (N = 84)	ETS < 30% (N = 70)	ETS ≥ 30% (N = 32)	ETS < 30% (N = 33)	ETS ≥ 30% (N = 329)	ETS < 30% (N = 330)
DpR (%), median (IQR)	66 (54-78)	28 (8-46)	68 (50,100)	31 (18-54)	74 (59-86)	31 (16-59)	68 (54-82)	29 (11-50)
Time from primary tumor to metastasis (mos), median (IQR)	20 (12-37)	25 (14-40)	26 (14-37)	26 (19-42)	NA	NA	20 (12-37)	26 (15-42)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: DpR = depth of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ETS = early tumor shrinkage; FOLFIRI = fluorouracil, leucovorin, and irinotecan; FOLFOX = fluorouracil, leucovorin, and oxaliplatin; IQR = interquartile range; mFOLFOX6 = modified FOLFOX; NA = not available.

In patients with symptoms at baseline, the median (95% CI) time to onset of any of the symptoms assessed by the composite endpoint was longer in patients with ETS ≥ 30% compared to ETS < 30%; however, the difference was not significant (2.3 [1.4-3.6] months for patients with ETS ≥ 30% and 1.6 [1.0-2.3] months for patients with ETS < 30%; HR [95% CI], 0.97 [0.70-1.34], $P = .8479$). Overall, the median time to onset of symptoms was shorter in these symptomatic patients compared to patients without symptoms at baseline. In patients without symptoms at baseline, the median (95% CI) time to onset of any of the symptoms included in the composite endpoint was longer in patients with ETS ≥ 30% compared to ETS < 30% (7.2 [5.3-10.3] vs. 4.8 [3.4-6.2] months; HR [95% CI], 0.76 [0.60-0.97], $P = .0277$).

In patients with symptoms at baseline, median time to onset of any of the symptoms included in the composite endpoint was longer in patients with DpR 73-100% (2.8 months) versus DpR < 0% (0.7 months); however, this did not reach statistical significance (Figure 4A; of note, in this analysis, the DpR < 0% subgroup lacked statistical power because of the small sample size). In patients without symptoms at baseline, greater DpR was associated with delayed median (95% CI) time to onset of any of the symptoms included in the composite endpoint (7.4 [4.9-21.7] vs. 1.8 [0.9-3.9] months for patients with DpR 73-100% vs. those with DpR < 0%; HR [95% CI], 0.41 [0.25-0.65], $P = .0002$) (Figure 4B).

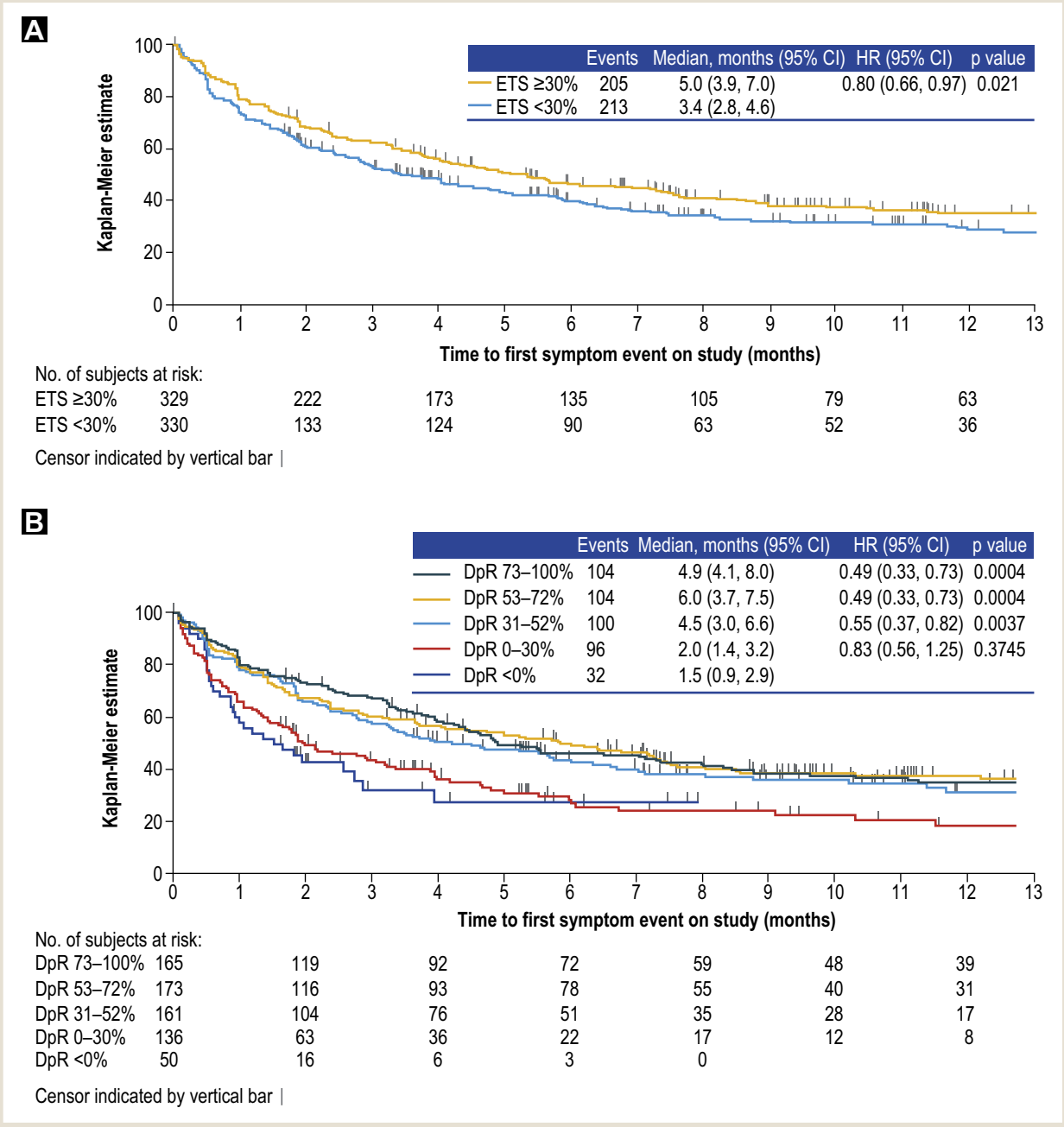
Discussion

We conducted additional analyses of the panitumumab PRIME, PEAK, and 314 studies, all of which were performed in patients with previously untreated mCRC and *RAS* WT tumors. The main objective of these analyses was to determine whether an early response to treatment, assessed by either ETS or DpR, may be related to the time to occurrence of symptoms during study treatment.

Overall, we found that onset of new symptoms was delayed in *RAS* WT mCRC patients who experienced ETS ≥ 30% relative to those who did not. The onset of new tumor-related symptoms was also delayed in patients who experienced greater DpR. These findings are consistent with our expectations, namely that an early response to treatment and tumor shrinkage might be predicted to lead to better symptom control than if no such response occurred. The correlation between tumor response and pain in mCRC has been noted previously.[27] Moreover, a 2017 study that examined effectiveness outcomes in a real-world oncology setting found that disease progression was associated with worsening symptoms and health-related QoL.[28] It follows that improved effectiveness outcomes should reduce symptoms and confer QoL benefits. Of note, it has been reported that both ETS and DpR are associated with improved progression-free survival, OS, and resection rates.[14,15] We also found that changes in ECOG PS were related to whether a treatment response was observed by ETS or DpR, in line with the expectation that all symptoms could affect ECOG PS.

In general, patients who were symptomatic at baseline had a poorer prognosis than those who were asymptomatic. However, experiencing ETS ≥ 30% improved OS in these patients so that it was comparable with OS in patients with ETS ≥ 30% and without symptoms at baseline. This is consistent with increased ETS leading to improved QoL in patients with symptoms at baseline.[16] Because

Figure 1 Kaplan-Meier Plots Showing Time to Occurrence of Any New Symptomatic Event (Composite Endpoint) for Pooled Data From PRIME, PEAK, and Study 314 by (A) ETS Status and (B) DpR



Abbreviations: ETS = early tumor shrinkage; CI = confidence interval; DpR = depth of response; HR = hazard ratio.

systemic anti-EGFR–targeted therapy is associated with ETS and DpR, patients both with and without symptoms at baseline may benefit from intensive systemic therapy to facilitate higher cytoreduction, in line with current recommendations from the European Society for Medical Oncology.[2,14] These recommendations highlight the fact that intensive systemic therapy is clinically relevant when conversion to resectable disease is the goal and for those patients who require a rapid reduction in tumor burden due to severe symptoms.[2] Indeed, severe symptoms may be indicative of impending clinical threat and the need for clinically relevant tumor shrinkage. However, intensive treatment may not be suitable for all patients—for example, those who are frail or who have comorbidities. In such patients, disease control is often the goal.[2]

Of note, the VOLFI trial found that intensive first-line therapy with FOLFOXIRI plus panitumumab resulted in high response rates with promising efficacy in right-sided and *BRAF*-mutated mCRC, although the number of patients analyzed in these subgroups was small.[29] In retrospective analyses of the TRIBE trial,

Table 2 Time to Occurrence of New Symptomatic Events for Pooled Data From PRIME, PEAK, and Study 314, by ETS Status

Characteristic	No. of Events	KM (Months) Median (95% CI)	Adjusted HR (95% CI)	*P*	Patients Without Symptoms (%) (KM Estimate) at:	
					6 Months	12 Months
All Symptoms						
ETS ≥ 30%	205	5.0 (3.9-7.0)			46.1	35.0
ETS < 30%	213	3.4 (2.8-4.6)	0.80 (0.66-0.97)	.0213	39.6	28.6
New Opiate Use						
ETS ≥ 30%	113	NE (31.2-NE)			75.9	66.0
ETS < 30%	128	27.4 (10.8-NE)	0.71 (0.55-0.92)	.0090	69.7	55.2
Weight Loss						
ETS ≥ 30%	84	NE (NE-NE)			81.0	71.8
ETS < 30%	107	NE (NE-NE)	0.64 (0.48-0.85)	.0022	68.5	62.0
Anemia						
ETS ≥ 30%	48	NE (NE-NE)			88.8	85.1
ETS < 30%	65	NE (NE-NE)	0.60 (0.41-0.88)	.0079	82.9	77.3
Asthenia						
ETS ≥ 30%	114	NE (33.8-NE)			71.3	62.7
ETS < 30%	124	NE (13.1-NE)	0.77 (0.60-1.00)	.0492	65.3	58.3
ECOG PS Decline						
ETS ≥ 30%	156	13.9 (8.6-NE)			61.7	51.6
ETS < 30%	157	7.9 (6.3-14.3)	0.87 (0.69-1.08)	.2042	57.0	46.1

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; ETS = early tumor shrinkage; HR = hazard ratio; KM = Kaplan-Meier; NE = not evaluable.

triplet chemotherapy plus bevacizumab improved ETS and DpR compared to doublet chemotherapy plus bevacizumab and provided survival benefits to patients with right- versus left-sided tumors independent of their *RAS* and *BRAF* status.[15,22] Improved efficacy was also observed with FOLFOXIRI plus bevacizumab versus FOLFOX plus bevacizumab in analyses of the STEAM trial.[30] It is therefore possible that a more intensive chemotherapy regimen, by inducing tumor shrinkage, may reduce tumor-related symptoms in patients with mCRC, including those with right-sided or *RAS*-/*BRAF*-mutated tumors.

The evolution of tumor-related symptoms over time has not been well studied in patients with mCRC. The data reported here provide further insights into the relationship between tumor response and tumor-related symptoms through analyses of a large *RAS* WT mCRC patient population receiving first-line panitumumab. To our knowledge, these are the first analyses to examine the relationship among ETS, DpR, and the occurrence of new tumor-related symptoms in mCRC. Importantly, the results reveal concordance between tumor response and time to occurrence of individual and composite tumor-related symptoms and ECOG PS decline, and we have demonstrated that a novel composite endpoint can be used to model tumor-related symptoms.

This study is limited by its retrospective design and the pooling of trials with different study designs. However, all 3 studies included assessment of tumor response per the modified RECIST criteria in their prospective design. Additional limitations include the relatively small number of patients included in 314 and the inclusion of only 41% of the total patient population for the 3 studies in these analyses, as this was the proportion of patients with *RAS* WT mCRC who also had data assessable for ETS. Prospective studies examining the relationship between markers of tumor response and the onset of symptoms are warranted.

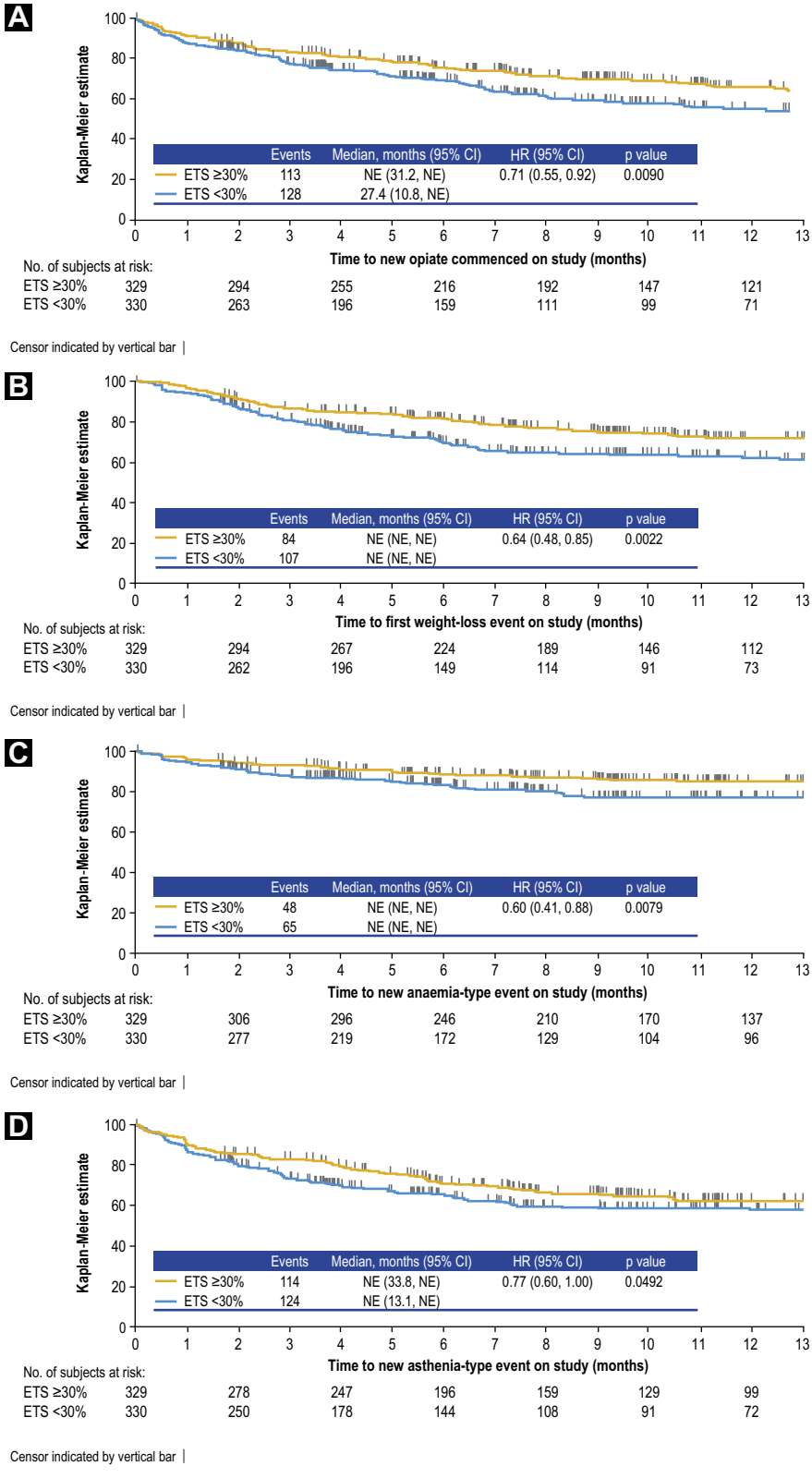
Conclusion

Our additional analyses of PRIME, PEAK, and Study 314 have identified ETS and DpR as measures of tumor response that not only correlate with OS and QoL, but also predict tumor-related symptomatic control in *RAS* WT mCRC patients. Regimens with high cytoreductive potential, such as panitumumab plus chemotherapy, may delay the onset of symptoms in this patient population and help to overcome the poor prognosis associated with mCRC for patients who present with tumor-related symptoms.

Availability of Data and Materials

There is a plan to share data. This may include deidentified individual patient data for variables necessary to address the specific research question in an approved data-sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data sharing requests relating to data in this article will be considered after the publication date and (1) this product and indication (or other new use) have been granted marketing authorization in both the United States and Europe, or (2) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen products and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements,

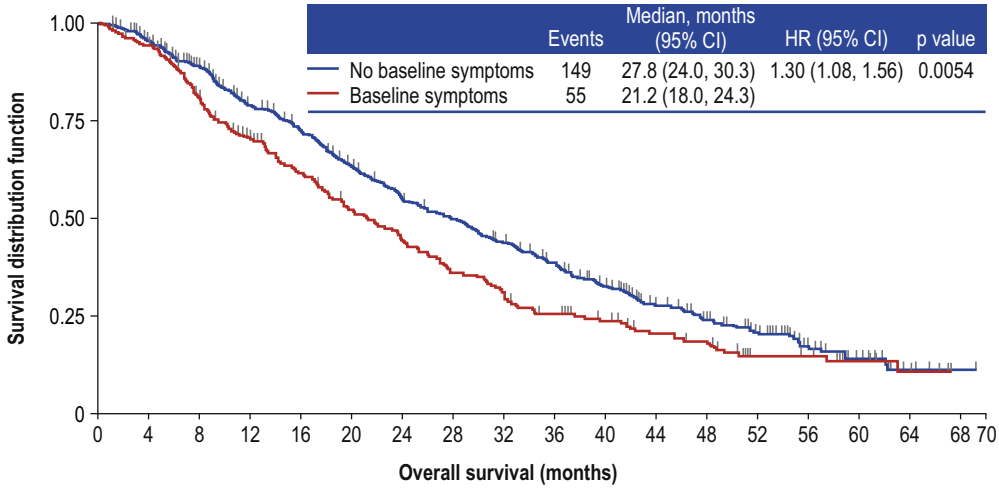
Figure 2 Kaplan-Meier Plots Showing Time to New Symptomatic Event by ETS Status for Pooled Data From PRIME, PEAK, and Study 314. (A) New Opiate Use, (B) First Weight Loss Event, (C) New Anemia, and (D) Asthenia-type Events



Abbreviations: CI = confidence interval; ETS = early tumor shrinkage; HR = hazard ratio; NE = not evaluable.

Figure 3 Kaplan-Meier Plots Showing Overall Survival for Pooled Data From PRIME, PEAK, and Study 314. Plots Are Shown by (A) Baseline Symptom and (B) Baseline Symptom and ETS Status

A



No. of subjects at risk:																		
No baseline symptoms	511	481	426	366	329	281	242	218	190	162	128	95	80	61	28	18	3	1
Baseline symptoms	223	208	169	141	120	100	85	69	58	47	40	31	25	13	12	8	4	0

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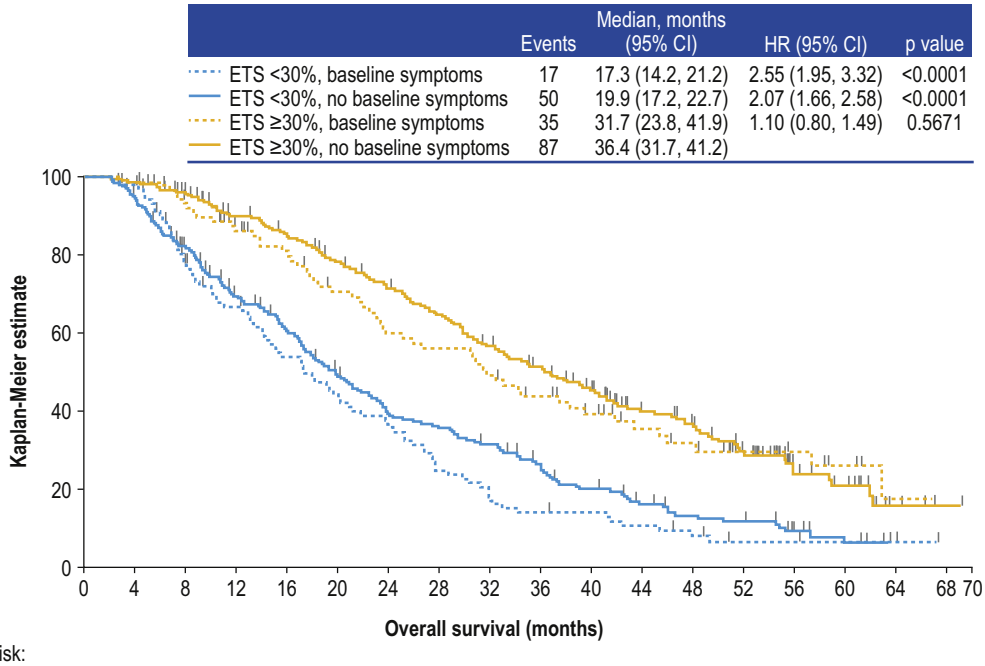
B



No. of subjects at risk:																		
ETS <30%, baseline symptoms	105	103	76	63	50	41	34	23	17	13	12	9	6	3	3	2	2	0
ETS <30%, no baseline symptoms	225	210	171	138	118	93	74	67	58	46	33	24	18	16	8	4	0	
ETS ≥30%, baseline symptoms	89	88	81	70	63	53	45	42	37	31	25	19	16	9	8	5	2	0
ETS ≥30%, no baseline symptoms	240	237	221	201	187	169	152	137	119	105	88	66	58	42	18	13	2	1

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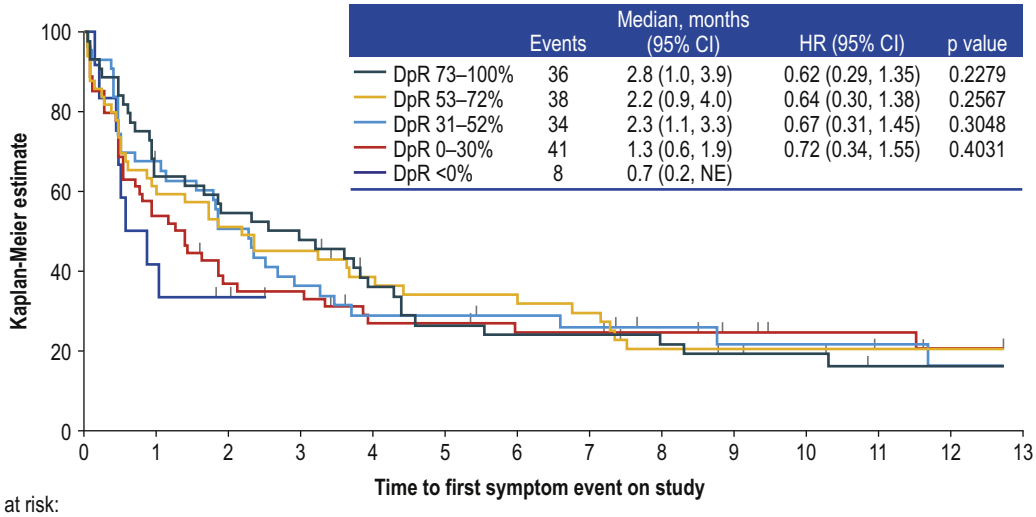
Abbreviations: CI = confidence interval; ETS = early tumor shrinkage; HR = hazard ratio.

Figure 4 Kaplan-Meier Plot Showing Time to Occurrence of Any New Symptomatic Events (Composite Endpoint) by DpR for Pooled Data From PRIME, PEAK, and Study 314. Data Shown for Patients (A) With Symptoms at Baseline and (B) Without Symptoms at Baseline

A



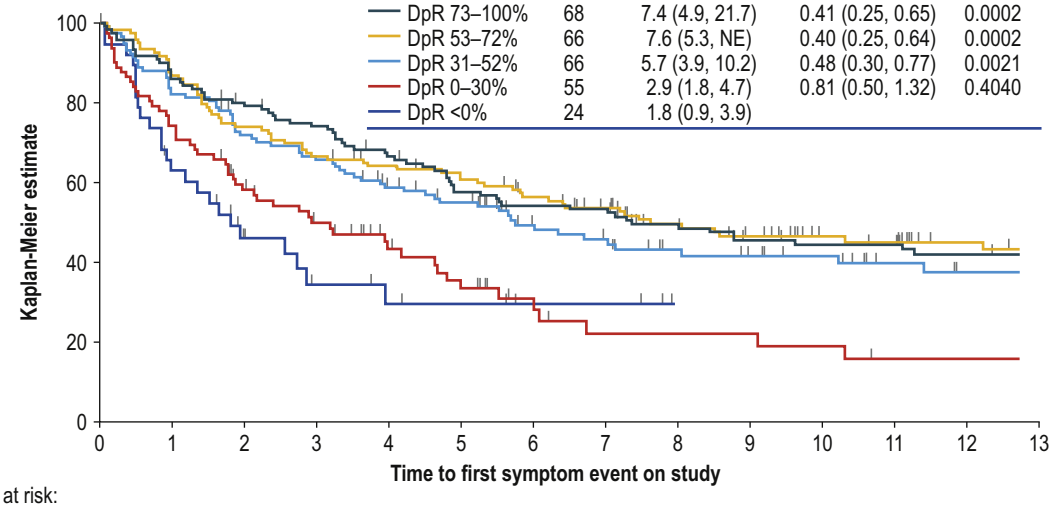
	Events	Median, months (95% CI)	HR (95% CI)	p value
DpR 73–100%	36	2.8 (1.0, 3.9)	0.62 (0.29, 1.35)	0.2279
DpR 53–72%	38	2.2 (0.9, 4.0)	0.64 (0.30, 1.38)	0.2567
DpR 31–52%	34	2.3 (1.1, 3.3)	0.67 (0.31, 1.45)	0.3048
DpR 0–30%	41	1.3 (0.6, 1.9)	0.72 (0.34, 1.55)	0.4031
DpR <0%	8	0.7 (0.2, NE)		

No. of subjects at risk:

DpR 73–100%	44	24	15	10	9	7	4
DpR 53–72%	49	25	17	15	8	7	6
DpR 31–52%	43	21	11	10	6	5	3
DpR 0–30%	54	19	13	11	10	6	4
DpR <0%	12	2					

Censor indicated by vertical bar |

B



	Events	Median, months (95% CI)	HR (95% CI)	p value
DpR 73–100%	68	7.4 (4.9, 21.7)	0.41 (0.25, 0.65)	0.0002
DpR 53–72%	66	7.6 (5.3, NE)	0.40 (0.25, 0.64)	0.0002
DpR 31–52%	66	5.7 (3.9, 10.2)	0.48 (0.30, 0.77)	0.0021
DpR 0–30%	55	2.9 (1.8, 4.7)	0.81 (0.50, 1.32)	0.4040
DpR <0%	24	1.8 (0.9, 3.9)		

No. of subjects at risk:

DpR 73–100%	121	95	77	62	50	41	35
DpR 53–72%	124	91	76	63	47	33	25
DpR 31–52%	118	83	65	41	29	23	14
DpR 0–30%	82	44	23	11	7	6	4
DpR <0%	38	14	6	3	0		

Censor indicated by vertical bar |

Abbreviations: CI = confidence interval; DpR = depth of response; HR = hazard ratio; NE = not evaluable.

publication plan, and qualifications of the researchers. In general, Amgen does not grant external requests for individual patient data for the purpose of reevaluating safety and efficacy issues already addressed in the product labeling. A committee of internal advisors reviews requests. If not approved, a data sharing independent review panel will arbitrate and make the final decision. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available online (http://www.amgen.com/datasharing).

Clinical Practice Points

- Both ETS and DpR have been associated with improved outcomes in retrospective analyses of first-line panitumumab mCRC studies. For patients with mCRC, QoL and tumor-related symptoms should be factored into treatment decisions.
- This retrospective analysis of 3 clinical studies of first-line panitumumab therapy in mCRC (PRIME, PEAK, and 314) aimed to investigate whether the occurrence of ETS and DpR in response to treatment is related to the time to occurrence of new symptoms.
- Patients were categorized into 2 groups on the basis of ETS status: $< 30\%$ and $\geq 30\%$. In a pooled analysis of 659 patients, the proportion of patients who experienced each new symptomatic event and ECOG PS decline was lower or the same in patients who experienced ETS $\geq 30\%$ versus those who did not.
- Time to onset of any of the assessed symptoms (as determined by a composite endpoint) was delayed in patients with ETS $\geq 30\%$ versus those with ETS $< 30\%$. Greater DpR was also associated with delayed onset of symptoms. The existence of tumor-related symptoms at baseline was associated with a poorer prognosis.
- The data reported here provide further insights into the relationship between tumor response and tumor-related symptoms through analyses of a large *RAS* WT mCRC patient population receiving first-line panitumumab.
- Because systemic anti-EGFR–targeted therapy is associated with ETS and DpR, patients both with and without symptoms at baseline may benefit from intensive systemic therapy to facilitate higher cytoreduction.

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Disclosure

J.T. has acted in consultancy and/or advisory roles for, and received honoraria from, Amgen, Celgene, Eli Lilly, Merck, Roche, Sanofi, Servier, Shire and Sirtex. M.G. has received research funding from and acted in consultancy/advisory roles for Amgen, Bayer, Merck, Roche and Sanofi. F.R. has received research funding from and/or acted on advisory boards for Amgen, Bayer, Celgene, Eli Lilly, Merck Serono, Merck Sharp & Dohme, Roche, Sanofi and Servier. M.K. has consulting/advisory roles and has participated in steering committees for Amgen and received travel/accommodation/expenses from Amgen. R.W. has acted in consultancy and/or advisory roles for, and received honoraria from, Amgen, BMS, CV6 Therapeutics, Merck Group and Servier, and has received travel/accommodation/expenses from Amgen. F.L. has no disclosures to report. T.P. has acted on advisory boards for Amgen, Merck Serono and Roche, and has received travel support from Amgen. M.T. was a contract worker for Amgen at the time the analyses were performed and now works for MT Statistics. P.B. is an employee of Amgen (Europe) GmbH and owns shares in Amgen. M.P. has received research funding from Amgen, Roche and Sirtex, and honoraria from Amgen, Merck Serono, Roche, Sanofi Aventis, Servier and Sirtex.

Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2019.07.009.

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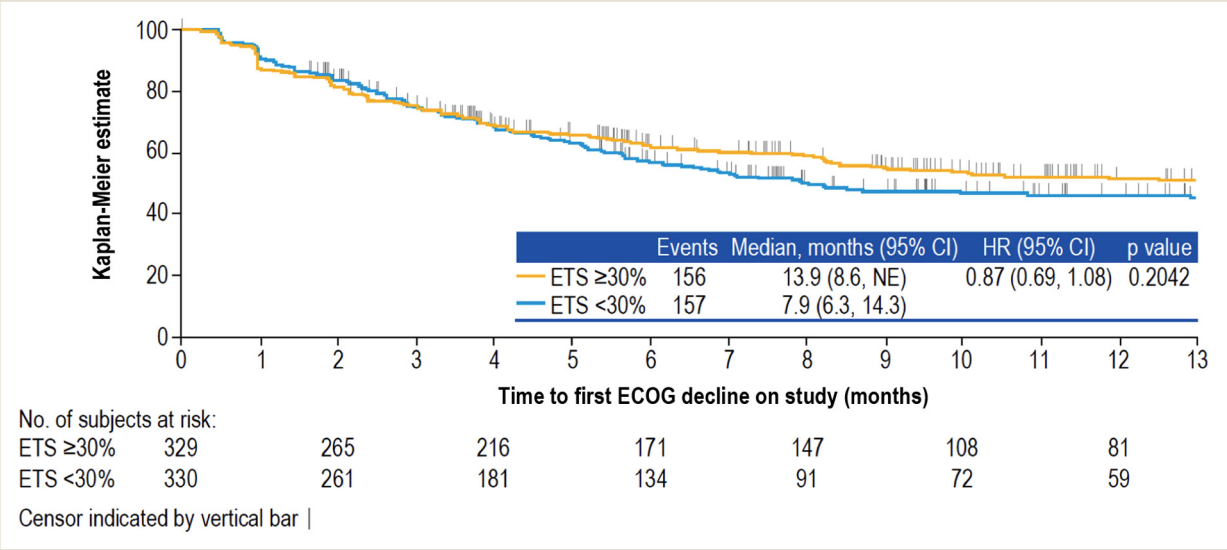
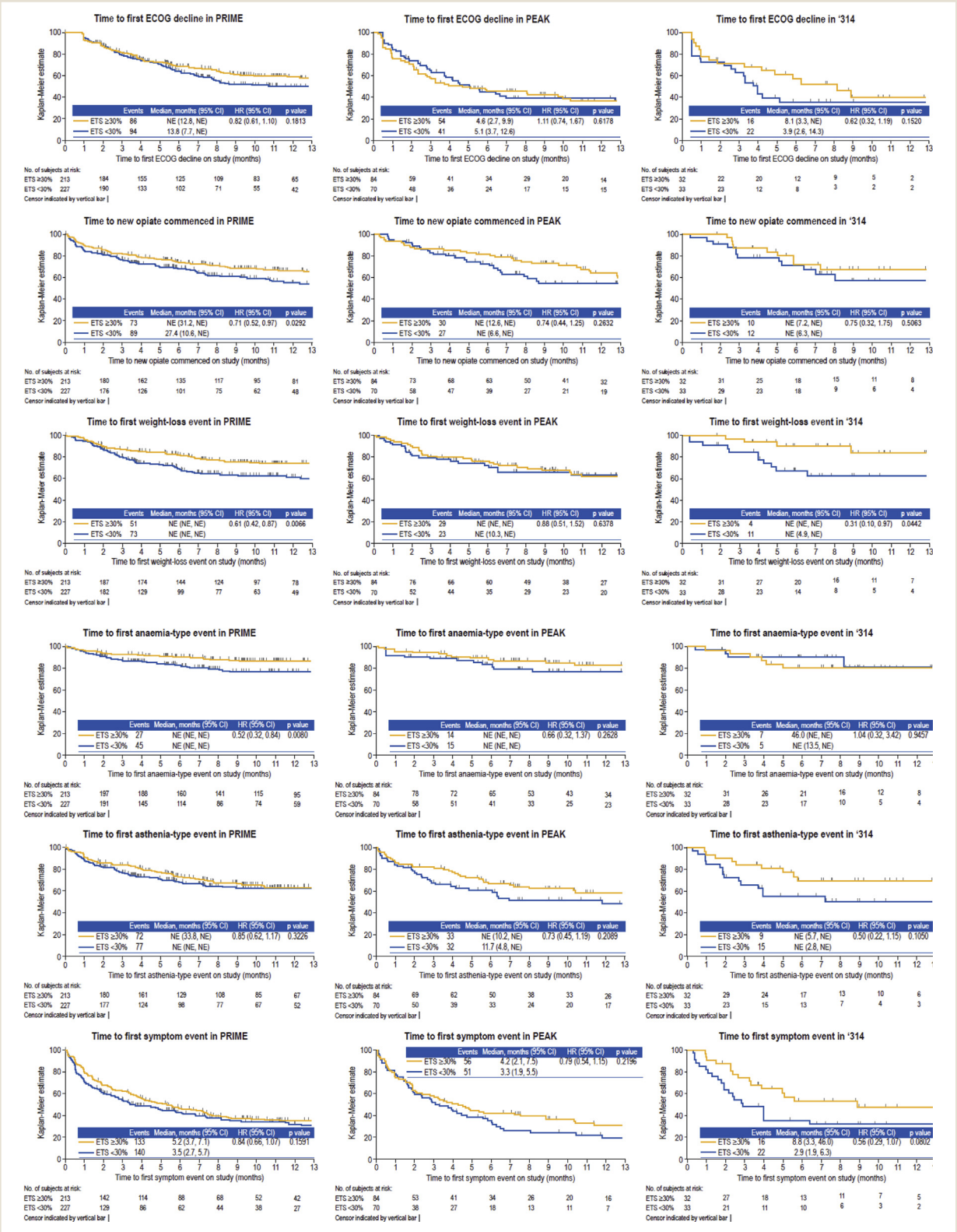
Supplemental Data

Supplemental Figure 1 Kaplan-Meier Plot Showing Time to Decline in ECOG PS by ETS Status for Pooled Data From PRIME, PEAK, and Study 314



Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; ETS = early tumor shrinkage; HR = hazard ratio; NE = not evaluable.

Supplemental Figure 2 Kaplan-Meier Plots Showing Time to New Symptomatic Event (ECOG PS Decline, New Opiate Use, First Weight Loss Event, New Anemia- or Asthenia-type Events, and Composite Endpoint) by ETS Status in PRIME, PEAK, and Study 314



Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; ETS = early tumor shrinkage; HR = hazard ratio; NE = not evaluable.

Supplemental Table 1 Definitions for Events at Baseline and New Events During Study Treatment

Event	Definition	
	Baseline	New Event on Study
Opiate use	Derived from concomitant medication start and stop dates. Opiates were selected by comparing the preferred term with those in the WHO Unified Medical Dictionary (version 9) and filtered for those of ATC classification system level 3 (pharmacologic subgroup) code "N02A"	Derived from concomitant medication start and stop dates. Opiates were selected by comparing the preferred term with those in the WHO Unified Medical Dictionary (version 9) and filtered for those of ATC classification system level 3 (pharmacologic subgroup) code "N02A"
Weight loss	Derived from medical history, searching for ongoing medical history events containing verbatim term string "anorex" / "annorex" / "appetit" / "hypophag" / "weight"	Weight decrease of $\geq$ 10% versus baseline or occurrence of AE with AEHLT "appetite disorders" or preferred term "weight decrease"
Anemia	Derived from medical history, searching for ongoing medical history events containing verbatim term string "anemia" / "anaemia" / "anemy" / "pancytop" / "paucytop" / "iron" / "transfus" / "thalasse," concomitant medicines for anemia taken within 2 weeks of study commencement or hemoglobin $<$ 90 g/L	Occurrence of AE with AEHLGT "anaemias nonhaemolytic" and "marrow depression," concomitant medicines for anemia provided during treatment (excluding prophylaxis), blood transfusion, hemoglobin $<$ 90 g/L or relevant AEs
Asthenia	Derived from medical history, searching for ongoing medical history events containing verbatim term string "asthe" / "asthae" / "astenia" / "fatig" / "fatiq" / "tired" / "weaknes"/ "malais" / "exhausti" / "feeling unwell"	Occurrence of AE with AEHLT "asthenic conditions"
ECOG PS	$\geq$ 1	Greater than baseline

Abbreviations: AE = adverse event; AEHLT = adverse event high-level term; AEHLGT = adverse event high-level group term; ATC = anatomic therapeutic chemical; ECOG PS = Eastern Cooperative Oncology Group performance status; WHO = World Health Organization.

Supplemental Table 2 Patients With Symptoms at Baseline and Who Developed New Symptoms During PRIME, PEAK, and Study 314 by ETS Status

Characteristic	PRIME		PEAK		Study 314		All Patients	
	ETS ≥ 30% (N = 213)	ETS < 30% (N = 227)	ETS ≥ 30% (N = 84)	ETS < 30% (N = 70)	ETS ≥ 30% (N = 32)	ETS < 30% (N = 33)	ETS ≥ 30% (N = 329)	ETS < 30% (N = 330)
Any baseline opiate use	29 (13.6)	37 (16.3)	14 (16.7)	13 (18.6)	3 (9.4)	6 (18.2)	46 (14.0)	56 (17.0)
New opiate usage on study	73 (34.3)	89 (39.2)	30 (35.7)	27 (38.6)	10 (31.3)	12 (36.4)	113 (34.3)	128 (38.8)
Any baseline asthenia	12 (5.6)	11 (4.8)	14 (16.7)	15 (21.4)	0	0	26 (7.9)	26 (7.9)
Asthenia event on study	118 (55.4)	126 (55.5)	60 (71.4)	51 (72.9)	17 (53.1)	22 (66.7)	195 (59.3)	199 (60.3)
Any baseline anemia	18 (8.5)	19 (8.4)	17 (20.2)	9 (12.9)	4 (12.5)	1 (3.0)	39 (11.9)	29 (8.8)
Anemia event on study	30 (14.1)	51 (22.5)	17 (20.2)	18 (25.7)	7 (21.9)	5 (15.2)	54 (16.4)	74 (22.4)
Baseline ECOG PS								
0	137 (64.3)	117 (51.5)	59 (70.2)	40 (57.1)	18 (56.3)	14 (42.4)	214 (65.0)	171 (51.8)
1	69 (32.4)	93 (41.0)	25 (29.8)	30 (42.9)	13 (40.6)	17 (51.5)	107 (32.5)	140 (42.4)
2	7 (3.3)	16 (7.0)	0	0	1 (3.1)	2 (6.1)	8 (2.4)	18 (5.5)
ECOG PS decline on study	86 (40.4)	94 (41.4)	54 (64.3)	41 (58.6)	16 (50.0)	22 (66.7)	156 (47.4)	157 (47.6)
Baseline anorexia	9 (4.2)	16 (7.0)	5 (6.0)	5 (7.1)	2 (6.3)	0	16 (4.9)	21 (6.4)
Weight event on study	88 (41.3)	101 (44.5)	45 (53.6)	37 (52.9)	7 (21.9)	14 (42.4)	140 (42.6)	152 (46.1)

Data are presented as n (%).
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; ETS = early tumor shrinkage.

Supplemental Table 3 Baseline Demographics and Disease Characteristics for Symptomatic Patients by ETS Status

Characteristic	PRIME		PEAK		Study 314		All Patients	
	ETS ≥ 30% (N = 48)	ETS < 30% (N = 66)	ETS ≥ 30% (N = 33)	ETS < 30% (N = 32)	ETS ≥ 30% (N = 8)	ETS < 30% (N = 7)	ETS ≥ 30% (N = 89)	ETS < 30% (N = 105)
Age (y), median (range)	56 (38-82)	58 (24-79)	57 (23-75)	61 (39-74)	65 (53-68)	52 (38-73)	56 (23-82)	59 (24-79)
Sex								
Female	21 (43.8)	24 (36.4)	17 (51.5)	11 (34.4)	2 (25.0)	2 (28.6)	40 (44.9)	37 (35.2)
Male	21 (43.8)	39 (59.1)	15 (45.5)	21 (65.6)	5 (62.5)	5 (71.4)	41 (46.1)	65 (61.9)
Treatment								
Panitumumab + FOLFIRI	0	0	0	0	7 (87.5)	7 (100.0)	7 (7.9)	7 (6.7)
Panitumumab + FOLFOX	24 (50.0)	23 (34.8)	0	0	0	0	24 (27.0)	23 (21.9)
Panitumumab + mFOLFOX6	0	0	24 (72.7)	12 (37.5)	0	0	24 (27.0)	12 (11.4)
Bevacizumab + mFOLFOX6	0	0	8 (24.2)	20 (62.5)	0	0	8 (9.0)	20 (19.0)
FOLFOX alone	18 (37.5)	40 (60.6)	0	0	0	0	18 (20.2)	40 (38.1)
***BRAF* Status**								
Mutant	3 (6.3)	11 (16.7)	2 (6.1)	2 (6.3)	1 (12.5)	3 (42.9)	6 (6.7)	16 (15.2)
Wild type	43 (89.6)	54 (81.8)	31 (93.9)	30 (93.8)	7 (87.5)	4 (57.1)	81 (91.0)	88 (83.8)
Unknown	2 (4.2)	1 (1.5)	0	0	0	0	2 (2.2)	1 (1.0)
Baseline ECOG PS								
0	19 (39.6)	19 (28.8)	17 (51.5)	17 (53.1)	3 (37.5)	3 (42.9)	39 (43.8)	39 (37.1)
1	19 (39.6)	34 (51.5)	15 (45.5)	15 (46.9)	4 (50.0)	4 (57.1)	38 (42.7)	53 (50.5)
2	4 (8.3)	9 (13.6)	0	0	0	0	4 (4.5)	9 (8.6)
Missing	6 (12.5)	4 (6.1)	1 (3.0)	0	1 (12.5)	0	8 (9.0)	4 (3.8)
Resection	9 (18.8)	4 (6.1)	3 (9.1)	3 (9.4)	3 (37.5)	0	15 (16.9)	7 (6.7)
Complete	7 (14.6)	3 (4.5)	2 (6.1)	2 (6.3)	1 (12.5)	0	10 (11.2)	5 (4.8)
Sites of Metastasis								
Liver + other	28 (58.3)	49 (74.2)	18 (54.5)	15 (46.9)	4 (50.0)	2 (28.6)	50 (56.2)	66 (62.9)
Liver only	7 (14.6)	6 (9.1)	9 (27.3)	7 (21.9)	3 (37.5)	3 (42.9)	19 (21.3)	16 (15.2)
Other only	7 (14.6)	8 (12.1)	5 (15.2)	10 (31.3)	0	2 (28.6)	12 (13.5)	20 (19.0)
Tumor Side								
Left	28 (58.3)	36 (54.5)	20 (60.6)	24 (75.0)	6 (75.0)	5 (71.4)	54 (60.7)	65 (61.9)
Right	11 (22.9)	14 (21.2)	8 (24.2)	6 (18.8)	0	0	19 (21.3)	20 (19.0)
Unknown	9 (18.8)	16 (24.2)	5 (15.2)	2 (6.3)	2 (25.0)	2 (28.6)	16 (18.0)	20 (19.0)
DpR (%), median (IQR)	65 (55-73)	28 (6-48)	79 (49-89)	28 (19-52)	76 (59-92)	17 (15-59)	67 (53-86)	27 (14-49)
Time from primary tumor to metastasis (mos), median (IQR)	20 (12-29)	14 (12-19)	36 (3-37)	28 (18-45)	NA	NA	21 (6-36)	19 (12-42)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: DpR = depth of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ETS = early tumor shrinkage; FOLFIRI = fluorouracil, leucovorin, and irinotecan; FOLFOX = fluorouracil, leucovorin, and oxaliplatin; IQR = interquartile range; mFOLFOX6 = modified FOLFOX; NA = not available.